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ART UNIT	PAPER NUMBER
1644	34

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/141,220	BANNON ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/29/02; 9/18/00; 9/29/00; 1/5/01; 8/13/01 .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 37-62 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 37-62 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 28 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 37-62 are pending.

2. The following new grounds of rejection are necessitated by the amendment filed 8/29/02.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 37-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method of making *any* modified allergen, *any* modified food allergen and *any* modified peanut allergen as set forth in claims 37-62. The instant claims are drawn to a method of making a modified protein allergen less reactive with IgE wherein the modified allergen is based on protein from a wide range of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes recited in claim 49 and encompassed by claim 37.

The specification discloses only a method of making modified peanut allergens selected from the group consisting of Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a reduced IgE binding whereas substituting alanine for arginine of Ara h1 lead to an increased IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that

the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

However, the specification as filed has not disclosed any specific protein from a wide range of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes which has the properties of allergen, much less the specific IgE binding sites to which the recited method of modification of an allergen can applied. Thus the invention encompassing a method of modified any allergen, and any food allergen, other than the three Ara H peanut allergens, is not adequately described.

Further, the specification disclosed only three species of modified food allergens from only one genus, i.e. peanut, given the lack of a written description of any additional species of allergen, and food allergen encompassed by the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

5. Claims 57-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The recitation of "1-6 amino acid residues" in claim 57 has no support in the specification and the claims as originally filed.

The recitation of "1-5 amino acid residues" in claim 58 has no support in the specification and the claims as originally filed.

The recitation of "1-4 amino acid residues" in claim 59 has no support in the specification and the claims as originally filed.

The recitation of "1-3 amino acid residues" in claim 60 has no support in the specification and the claims as originally filed.

The recitation of "1-2 amino acid residues" in claim 61 has no support in the specification and the claims as originally filed. Applicants have not pointed out the support for said "1-6, 1-5, 1-4, 1-3 and 1-2 amino acid residues" in at least one IgE epitope of any allergen, or any food allergen for the claimed method.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "substantially the same way as the unmodified allergen" in claims 38-39 is ambiguous and indefinite because the specification does not define the term "substantially". One of ordinary skill in the art cannot appraises the metes and bound of the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 37, 39-43, 46-47, 49-51, and 57-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892).

Aki *et al* teach a method of making modified allergen such as allergen Mag1E2 from house dust mite which is less reactive with IgE wherein the method comprises identifying one or more IgE binding sites in dust mite allergen by contacting the allergen with serum IgE from an individual or pooled serum from 8 mite-allergic patients (See page 359, column 2, page 360, column 1, in particular), modifying the allergen by mutating at least one amino acid in the center of IgE binding sites by site-directed mutagenesis such as substituting hydrophobic amino acid such as Ala, Leu, and Isolucine for neutral amino acid such as glycine or hydrophilic amino acid such as arginine (See page 361, column 1, page 360, column 1, last full paragraph, in particular).

The reference modified allergens have decrease IgE binding while IgG binding is substantially the same as the unmodified allergen (see page 361, column 1, third paragraph, in particular). The reference modified allergen is a portion of the allergen which corresponds to Ser56 to Lys70 or Asp104 to Ala 115 of the unmodified dust allergen (See page 360, column 1, third paragraph, in particular). The reference modified allergen is made in a recombinant host such as bacteria (See page 358, Materials and Methods, in particular). The reference modified allergen Mag1-E2 is twelve amino acids in length and each amino acid residue was replaced with Gly by site-directed mutagenesis (See page 361, column 1, identification of the residue that participates in Binding to Specific IgE antibody, Fig 1, in particular). Aki *et al* further teach that site-directed mutagenesis in combination with IgE binding as measured by colony blot test would be effective for determining which amino acid residues in each epitope are important for the specificity of allergic sera (See page 363, column 1, in particular). Thus, the reference teachings anticipate the claimed invention.

10. Claims 37-38, 41-43, 45-47, 49-51 and 57-62 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,547,669 (Aug 1996, PTO 892).

The '669 patent teaches a method of making modified protein allergen such as recombitope peptide of FEL DI from a mammal such as cat, whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that modified protein binding to IgE is reduced (See column 3, lines 36-45, in particular) and maintains T cell activity (See column 14, lines 12-13, column 17-18, column 2, summary of invention, in particular). The reference method of making the reference modified protein allergen (recombitope peptide) comprises identified allergen which is less reactive with IgE, substituting at least one amino acid for neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituting with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular). The reference method wherein the modified protein allergen is expressed recombinantly in host cell such as bacteria (E coli) or is made in cells using site specific mutagenesis (column 16, line 1, in particular), and the reference method further comprises screening the modified protein allergen for stimulating T cell activity such as T cell proliferation better than unmodified protein allergen (See column 24, lines 8-67, bridging column 25, lines 1-32, in particular), initiating delayed type sensitivity which is Th-1 response (See column 26, lines 60-62, in particular) and reducing IgE binding (See column 22, lines 44, column 23, lines 59-61,

in particular). The '669 patent further teaches a method for designing recombitope peptides of any allergen where the protein antigen to which the individual is senstive has unknown or ill-defined epitope (See abstract, in particular) and the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Thus, the reference teachings anticipate the claimed invention.

11. The filing date of the instant claims 56-61, is deemed to be the filing date of the priority application 60/073,283, 60/074,633, 60/074,624, 60/074,590 all filed Feb 13, 1998, because USSN 08/717,933 filed Sept 23, 1996 do not support the claimed limitations of "Ara h3, " in claims 56 "1-6 amino acid residues" in claim 57, 1-5 amino acid residues" in claim 58, 1-4 amino acid residues" in claim 59, 1-3 amino acid residues" in claim 60, 1-2 amino acid residues" in claim 61 in any one IgE epitope of any allergen as encompassed by the claimed method. The 08/717,933 discloses only the nucleotide molecules of the specific unmodified Ara h1 and Ara h2, the amino acid sequence of the specific modified peanut allergen Ara h1 and Ara h2 as well as antibody to Ara h1 and Ara h2 and a method of making said modified peanut allergens. Applicants are reminded that such priority for the instant limitations requires a written description and enablement under 35 U.S.C. § 112, first paragraph.

12. Claims 37, 40-43, 48-53, and 55-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449).

Burks *et al* teach a method of making a modified allergen such as peanut allergen Ara h1which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h1 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See page 334, Materials and Methods, in particular), modifying the reference peanut allergen by mutating in the center of at least one or more amino acid in one or more IgE sites by substituting a hydrophobic amino acid (Ala) for the neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, Fig 5, in particular), screening for IgE binding of modified allergen using serum IgE from an individual or pooled serum from 15 patient with peanut-hypersensitivity (See page 337, column 2, in particular) and selecting peptide such as peptides, 1, 3, 4, and 17 which have decrease IgE binding as compared to the control unmodified wild type allergen (See Fig 6 and 7, in particular). The reference method of making modified-allergen reduces IgE binding to less than about 1% of

that observed to the unmodified allergen (See Fig 4 and 5, in particular). The reference further teaches there are at least 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of said protein (See Figs 1-3, Fig 6, page 339, column 1, in particular). Burks *et al* teach it is possible to mutate the Ara h1 allergen to a protein so that it no longer binds IgE and this could be used to replace its allergenic homologue in the peanut genome to develop a hypoallergenic peanut and for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Claims 57-61 are included in this rejection because the reference teaches there are 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and anticipates the term "at least one" amino acids in at least one IgE epitope of the allergen. The reference method teaches that the modified peanut allergen is useful for developing a hypoallergenic peanut for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Thus, the reference teachings anticipate the claimed invention.

13. Claims 37, 40-43, 48-53, and 55-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449).

Stanley *et* teach a method of making a modified allergen such as peanut allergen Ara h2 which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h2 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See entire document, Fig 2, Abstract, in particular), modifying the reference peanut allergen by mutating in the center of at least one or more amino acid in one or more IgE sites by substituting a hydrophobic amino acid (Ala) for the neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 5, in particular), screening for IgE binding of modified allergen using serum IgE from an individual or pooled serum from 15 patient with peanut-hypersensitivity (see caption of Fig 5, in particular), and selecting peptide such as peptides 3, 6 and 7 which have decrease IgE binding as compared to the control unmodified wild type allergen (See Figs 4 and 5, page 251 column 1, in particular). The reference method of making modified-allergen reduces IgE binding to less than about 1% of that observed to the unmodified allergen (See Fig 4 and 5, in particular). The reference further teaches there are at least ten different IgE binding epitopes on peanut allergen Ara h2 distributed throughout the protein and the modified allergen is a portion of said protein (See page 251, column 2, first full paragraph, in particular).

Stanley *et al* teach it is possible to mutate the Ara h2 allergen to a protein so that it no longer binds IgE and this could be for desensitization immunotherapy (See page 252, first paragraph, in particular). Claims 57-61 are included in this rejection because the reference teaches there are 10 different IgE binding epitopes on peanut allergen Ara h2 distributed throughout the protein and anticipates the term "at least one" amino acids in at least one IgE epitope of the allergen. Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 37-38 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of WO 94/11512 publication (May 1994, PTO 892)

The teachings of Aki *et al* have been discussed supra.

The claimed invention as recited in claim 38 differs from the teachings of the reference only that the method further comprising screening for activation of T cells that have been cultured from an individual that is allergic to the allergen and selecting the modified allergens which activate the T cells in substantially the same way as the unmodified allergen.

The claimed invention as recited in claim 49 differs from the teachings of the reference only that the method wherein the modified allergen is based on a protein obtained from trees.

WO 94/11512 publication teaches a method of making modified allergen from tree such as Cryptomeria japonica major pollen allergen Cry j II by screening for IgE binding (See page 36, Example 6) and T cell activation such as T cell proliferation assays and selecting modified allergen which activate T cells equal to or greater than 2 times the background level of the background control peptide (See page 38-39, page 8, lines 9-18, in particular). WO 94/11512 publication teaches that the reference Cry j II peptide fragment is useful for diagnosing, and treating Japanese cedar pollinosis (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screening for activation of T cells that have been cultured from an individual that is allergic to the allergen as taught by the WO 94/11512 for a method of making modified allergen as taught by Aki *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 94/11512 publication teaches that modified allergen containing T cell epitope with minimal IgE stimulating activity is desirable for diagnosing, and treating Japanese cedar pollinosis (See abstract, page 8, 29-36, in particular).

17. Claims 37 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of US Pat No 6,207,646 B1 (March 2001; PTO 892).

The teachings of Aki *et al* have been discussed supra.

The claimed invention as recited in claim 44 differs from the teachings of the reference only that the method wherein the modified allergen is formulated with an adjuvant such as IFNγ or immune stimulatory sequence oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1 type response.

The '646 patent teaches adjuvant such as nucleic acids containing unmethylated CpG motifs for stimulating Th1 immune response such as the production of Th1 cytokines such as IL-12, and IFNγ that suppress Th2 immune response such as inhibiting the production of IL-4 (See entire document, Abstract, column 6, lines 10-15, in particular). The reference nucleic acids are useful for desensitization therapy to treat or prevent the occurrence of an allergic reaction (See column 6, lines 59-65, claim 3 of '646, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include immune stimulatory sequence oligodeoxynucleotide sequences containing unmethylated CpG motifs for stimulating Th1 immune response such as the production of Th1 cytokines such as IL-12, and IFNγ that suppress Th2 immune response such as inhibiting the production of IL-4 as taught by the '646 patent (See entire document, Abstract, column 6, lines 10-15, in particular) in the method of making any modified allergen as taught by Aki *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '646 patent teaches adjuvant such as nucleic acids containing unmethylated CpG motifs skew the immune response toward Th1 immune response and is useful for desensitization therapy or to treat the occurrence of an allergic reaction (See column 6, lines 59-65, claim 3 of '646, in particular). Aki et al teach that site-directed mutagenesis in combination with IgE binding as measured by colony blot test would be effective for determining which amino acid residues in each epitope are important for the specificity of allergic sera (See page 363, column 1, in particular).

18. Claims 37, 48, and 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449), or Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449) or US Pat No. 5,449,669 (Sept 1995, PTO 892).

The teachings of Aki *et al* have been discussed supra.

The claimed invention as recited in claims 48 and 56 differs from the teachings of the reference only that the method wherein the modified allergen is made from a peanut allergen selected from Ara h1 or Ara h2.

The claimed invention as recited in claim 52 differs from the teachings of the reference only that the method is a method of making modified food allergen.

The claimed invention as recited in claim 53 differs from the teachings of the reference only that the method wherein the modified allergen is from crustaceans.

The claimed invention as recited in claim 54 differs from the teachings of the reference only that the method wherein the modified allergen is shrimp.

The claimed invention as recited in claim 55 differs from the teachings of the reference only that the method is a method of making modified peanut allergen.

Burks *et al* teach a method of making a modified allergen such as peanut allergen Arah1which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h1 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See page 334, Materials and Methods, in particular), modifying the reference peanut allergen by mutating in the center of at least one amino acid in one or more IgE sites by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites with a neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, Fig 5, in particular). The reference method screens for IgE binding of modified allergen using serum IgE from an individual or pooled serum from 15 patient with peanut-hypersensitivity (See page 337, column 2, in particular) and selects peptide such as peptides, 1, 3, 4, and 17 which have decrease IgE binding as compared to the control or unmodified wild type allergen (See Fig 6 and 7, in particular). The reference method of making modified-allergen is useful for making hypoallergenic peanut that could blunt allergic reactions in sensitive individual (See page 339, column 1, in particular).

Stanley *et al* teach a method of making a modified food allergen such as peanut allergen Arah2 which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h2 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See entire document, Fig 2, Table III, Abstract, in particular). The reference modified peanut allergen such as Ara h 2 peptides have been mutated by alanine amino acid substitution and no longer bind IgE when contacted with serum IgE from individual or pooled serum of individuals who are allergic to peanut allergen (See Fig 5, in particular). The reference method of making modified-allergen is useful for allergen immunotherapy that could blunt allergic reactions in sensitive individual (See page 251, column 2, in particular).

The 5,449,669 patent teaches unmodified food allergen from crustacean such as shrimp and IgE binding epitopes (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substituted the house dust mite allergen in the method of making modified allergen as taught by Aki et al for the peanut allergen such as Ara h1 as taught by Burkes et al or

the peanut allergen such as Ara h2 by Stanley *et al* or the shrimp allergen as taught by the '5,449,669 patent for a method of modified any food allergen. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the 5,449,669 patent teaches IgE epitopes are useful in diagnosis and/or treatment of allergies. Burks *et al* teach that it is possible to mutate any allergen to a protein so that it no longer binds IgE for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Stanley *et al* teach that peanuts are a major cause of serious allergic reactions and modified peanut allergen is useful for allergen immunotherapy that could blunt allergic reactions in sensitive individual (See page 251, column 2, in particular). The 5,449,669 patent teaches unmodified food allergen from crustacean such as shrimp and IgE binding epitopes (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies. Aki et al teach that site-directed mutagenesis in combination with IgE binding as measured by colony blot test would be effective for determining which amino acid residues in each epitope are important for the specificity of allergic sera (See page 363, column 1, in particular).

19. Claims 37, 39-40 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,547,669 patent (Aug 1996, PTO 892) in view of Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) and US Pat No 6,207,646 B1 (March 2001; PTO 892).

The teachings of the 5,547,669 patent have been discussed supra.

The claimed invention as recited in claim 39 differs from the teachings of the reference only that the method further comprising screening for binding of the modified allergen to IgG using serum IgG from an individual that is allergic to the allergen and selecting the modified allergens which bind to IgG in substantially the same way as the unmodified allergen.

The claimed invention as recited in claim 40 differs from the teachings of the reference only that the method wherein the modified allergen is mutated in the center of one or more of the IgE binding sites.

The claimed invention as recited in claim 44 differs from the teachings of the reference only that the method wherein the modified allergen is formulated with an adjuvant such as IFNγ

or immune stimulatory sequence oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1 type response.

Aki *et al* teach a method of making modified allergen such as allergen Mag1E2 from house dust mite which is less reactive with IgE wherein the method comprises identifying one or more IgE binding sites in dust mite allergen by contacting the allergen with serum IgE from an individual or pooled serum from 8 mite-allergic patients (See page 359, column 2, page 360, column 1, in particular), modifying the allergen by mutating at least one amino acid in the center of IgE binding sites by site-directed mutagenesis such as substituting hydrophobic amino acid such as Ala, Leu, and Isolucine for neutral amino acid such as glycine or hydrophilic amino acid such as arginine (See page 361, column 1, page 360, column 1, last full paragraph, in particular). The reference-modified allergens have decrease IgE binding while IgG binding is substantially the same as the unmodified allergen (see page 361, column 1, third paragraph, in particular).

The 6,207,646 patent teaches adjuvant such as nucleic acids containing unmethylated CpG motifs for stimulating Th1 immune response such as the production of Th1 cytokines such as IL-12, and IFNγ that suppress Th2 immune response such as inhibiting the production of IL-4 (See entire document, Abstract, column 6, lines 10-15, in particular). The reference nucleic acids are useful for desensitization therapy to treat or prevent the occurrence of an allergic reaction (See column 6, lines 59-65, claim 3 of '646, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include screening IgG from an individual that is allergic to the allergen and selecting the modified allergens which bind IgG in substantially the same way as the unmodified allergen as taught by the Aki et al and formulating the modified allergen with an adjuvant such as the immune stimulatory sequence oligodeoxynucleotide sequences containing unmethylated CpG motifs for stimulating Th1 immune response such as the production of Th1 cytokines such as IL-12, and IFNγ that suppress Th2 immune response such as inhibiting the production of IL-4 as taught by the 6,207,646 patent (See entire document, Abstract, column 6, lines 10-15, in particular) in the method of making any modified allergen as taught by Aki *et al* and the 6,207,646 and 5,547,669 patents. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the 6,207,646 patent teaches adjuvant such as nucleic acids containing unmethylated CpG motifs

skew the immune response toward Th1 immune response and is useful for desensitization therapy or to treat the occurrence of an allergic reaction (See column 6, lines 59-65, claim 3 of '646, in particular). Aki et al teach that site-directed mutagenesis in combination with IgE binding as measured by colony blot test and IgG would be effective for determining which amino acid residues in each epitope are important for the specificity of allergic sera (See page 363, column 1, in particular).

20. Claims 37, 48, 52-53 and 54-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,547,669 patent (Aug 1996, PTO 892) in view of Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449), or Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449) or US Pat No. 5,449,669 (Sept 1995, PTO 892).

The teachings of the 5,547,669 patent have been discussed supra.

The claimed invention as recited in claims 48 and 56differs from the teachings of the reference only that the method wherein the modified allergen is made from a peanut allergen selected from Ara h1 or Ara h2.

The claimed invention as recited in claim 52 differs from the teachings of the reference only that the method is a method of making modified food allergen.

The claimed invention as recited in claim 53 differs from the teachings of the reference only that the method wherein the modified allergen is from crustaceans.

The claimed invention as recited in claim 54 differs from the teachings of the reference only that the method wherein the modified allergen is shrimp.

The claimed invention as recited in claim 55 differs from the teachings of the reference only that the method is a method of making modified peanut allergen.

Burks *et al* teach a method of making a modified allergen such as peanut allergen Arah1which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h1 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See page 334, Materials and Methods, in particular), modifying the reference peanut allergen by mutating in the center of at least one amino acid in one or more IgE sites by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites with a neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, Fig 5, in particular). The reference method screens for IgE binding of modified allergen using serum IgE from an individual or pooled serum from 15 patient

with peanut-hypersensitivity (See page 337, column 2, in particular) and selects peptide such as peptides, 1, 3, 4, and 17 which have decrease IgE binding as compared to the control or unmodified wild type allergen (See Fig 6 and 7, in particular). The reference method of making modified-allergen is useful for making hypoallergenic peanut that could blunt allergic reactions in sensitive individual (See page 339, column 1, in particular).

Stanley *et al* teach a method of making a modified food allergen such as peanut allergen Arah2 which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h2 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See entire document, Fig 2, Table III, Abstract, in particular). The reference modified peanut allergen such as Ara h 2 peptides have been mutated by alanine amino acid substitution and no longer bind IgE when contacted with serum IgE from individual or pooled serum of individuals who are allergic to peanut allergen (See Fig 5, in particular). The reference method of making modified-allergen is useful for allergen immunotherapy that could blunt allergic reactions in sensitive individual (See page 251, column 2, in particular).

The 5,449,669 patent teaches unmodified food allergen from crustacean such as shrimp and IgE binding epitopes (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substituted the cat allergen in the method of making modified allergen as taught by 5,547,669 patent for the peanut allergen such as Ara h1 as taught by Burkes et al or the peanut allergen such as Ara h2 by Stanley *et al* or the shrimp allergen as taught by the '5,449,669 patent for a method of modified any food allergen. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the 5,449,669 patent teaches IgE epitopes are useful in diagnosis and/or treatment of allergies. Burks *et al* teach that it is possible to mutate any allergen to a protein so that it no longer binds IgE for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Stanley *et al* teach that peanuts are a major cause of serious allergic reactions and modified peanut allergen is useful for allergen immunotherapy that could blunt allergic reactions

in sensitive individual (See page 251, column 2, in particular). The 5,449,669 patent teaches unmodified food allergen from crustacean such as shrimp and IgE binding epitopes (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies. The '5,54769 patent further teaches a method for designing recombitope peptides of any allergen where the protein antigen to which the individual is senstive has unknown or ill-defined epitope (See abstract, in particular) and the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular). Thus, the reference teachings anticipate the claimed invention.

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

24. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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